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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/023,232	02/13/1998	ANN MONOSOV	312762001530	6662

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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 08/11/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/023,232

Applicant(s)

MONOSOV ET AL.

Examiner

Anne Marie S. Wehbe

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 May 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18,20-25,27,28,30-37,42-49 and 54-61 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18,20-25,27,28,30-37,42-49 and 54-61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. | 6) <input type="checkbox"/> Other: _____. |

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DETAILED ACTION

Applicant's arguments and the declaration by Robert Hoffman received on 5/20/02 have been entered. Claims 1-18, 20-25, 27-28, 30-37, 42-49, and 54-61 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 103

The rejection of claims 1-13, 15, 17-18, 20, 22, 24, 27-28, 30-37, 42-49, and 54-61 under 35 U.S.C. 103(a) as being unpatentable over Kyriazis et al. (1981) Canc. Res., Vol. 41, 3995-4000 in view of Otto et al. (1985) J. Urol., Vol. 134, 170-174, Wang et al. (1982) Exp. Cell. Biol., Vol. 50, 330-331, and McLemore et al. (1987) Cancer Research, Vol. 47(19), 5132-5140, is maintained. Applicant's arguments and the declaration by Dr. Hoffman have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of reasons of record as discussed in detail below.

The applicant argues that the combination of references cited do not provide motivation for making applicant's invention or predict the applicant's "highly successful" results. The

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applicant provides arguments which imply that none of the references individually anticipate applicant's invention, and that further none of the references individually provide an expectation of success in consistently reproducing the clinical pattern of metastasis of a human tumor in a nude mouse by orthotopically implanting human tumor pieces. Although applicant's arguments against the references individually will be addressed in detail, the applicant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, it is noted that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). It is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979) In the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors.

Regarding the teachings of Kyriazis et al., the applicant argues that the declaration by Dr. Hoffman provides Exhibit 2 which is supposed to represent a comparison of the results obtained by Kyriazis and the results obtained using applicant's "AntiCancer MetaMouse". The applicant

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argues that Exhibit 2 shows that the mouse model taught by Kyriazis et al. fails to demonstrate a clinical pattern of metastasis. The applicant has identified the alleged “clinical pattern of metastasis” as the pattern of metastasis taught by James E. Holland in a book entitled Cancer Medicine. 5th ed., B.C. Decker, Inc. (2000). Please note that neither the entire reference, Cancer Medicine, nor any of the specific chapters referenced by applicants have been provided to the examiner for consideration or made of record in the instant application. Further, based on the 2000 publication date of the Holland book, it is unclear whether the teachings in Holland reflect recent advances and observations in cancer research, or whether they are simply a recitation of observations which were known at or around the time of filing, 1988, which is 12 years earlier than the publication date of Holland. Thus, the relative importance of the “clinical pattern of metastasis” for various tumors listed in Exhibit 2, and Exhibit 3, cannot be determined.

Furthermore, Kyriazis et al. did not provide a complete work-up of the mice transplanted with human tumor fragments. Kyriazis et al. only provides data regarding metastasis to lymph nodes and lungs in Table 1. In Figures 5-6, and 8-13, Kyriazis et al. provides pictures of metastasis in the lung and lymph nodes. Only in Figures 7 and 8 does Kyriazis et al. mention metastasis to diaphragm (for the Capon-1 pancreatic adenocarcinoma) and the salivary gland (for the SW-800 bladder carcinoma). Although, as applicant suggests, other tissues may have been observed for metastasis, clearly Kyriazis et al. was interested in reporting on metastasis to lymph nodes and lung. The fact that Kyriazis et al. choose these organs to focus on does not teach away or preclude the ability of the transplanted tumors to form metastases in other locations. Furthermore,

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the metastasis reported by Kyriazis et al. do indeed match with locations of metastasis observed in human tumor patients. Kyriazis et al. reports that the SW-800 bladder tumor, implanted subcutaneously, metastasizes to the lymph nodes, salivary gland, and diaphragm, all locations identified by Holland et al. Likewise, Kyriazis et al. reports that the Capon-1 pancreatic adenocarcinoma metastasizes to the lymph nodes, lungs, and diaphragm, all locations identified by Holland et al. for pancreatic tumor metastases. Please note that applicant's Exhibit 2 errs by failing to include metastasis to the diaphragm for the Capon-1 tumor as taught by Kyriazis in Figure 7, page 3998. Thus, contrary to applicant's interpretation, Kyriazis et al. does in fact demonstrate that subcutaneous transplantation of human tumor pieces into nude mice results in a pattern of neoplastic growth that mimics that observed in human patients. The applicant is also reminded that the claims as written are not directed to the progression of metastatic growth, the claims as written recite rodent models for human **neoplastic** disease. Neoplastic disease refers to diseases which result from the inappropriate growth of certain cells. Neoplastic tissue or cells, while encompassing metastatic tissue or cells, encompasses a much wider variety of cells.

Furthermore, regarding metastasis in general, and patterns of metastasis, Kyriazis et al. also teaches that metastasis is an inconstant finding in humans, and that,

Although it is encountered in the majority of cancers, there are occasions where the most extensive search, even at the autopsy table, fails to reveal metastatic lesions in tumors otherwise characterized as having a rather aggressive behavior. This negative finding, however, does not rule out the presence of metastases since it is known that metastatic foci not seen at the time of the patient's treatment may become apparent years later ultimately contributing to the patient's death. It should be kept in mind that between the time of the inception of neoplasia to the stage of metastatic disease there is an interval of

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months or years. Detectable metastases for most tumors represent a late event. Therefore, their presence depends largely on the timing the neoplastic growth is taken under consideration.

(Kyriazis et al., page 3996, column 1).

From these teachings, it is clear that detecting all possible metastases in all possible locations is difficult and depends largely on when the search for metastases takes place and on the stage of the tumor itself. Therefore, although the RT-4 tumor tested by Kyriazis et al. did not appear to metastasize, Kyriazis is not surprised because of the origin of the tumor which is a Stage 1, Grade 1 bladder carcinoma. According to Kyriazis et al. , based on the Stage and Grade of this tumor, the growth of the RT-4 tumor in the Kyriazis et al. model mouse, “ recapitulat[es] in an exact manner the behavior of the same tumor in the human” (Kyriazis et al., page 2996, column 2, paragraph 2).

Finally, as noted above, Kyriazis et al. has not been applied as a 102 reference anticipating applicant’s invention as claimed. The rejection of record is based on 35 U.S.C. 103(a) and Kyriazis et al. has been cited as a primary reference, supplemented by the teachings of the secondary references Otto et al., Wang et al., and McLemore et al. Kyriazis et al. has therefore been relied upon for teaching a subcutaneous transplantation model of metastasis. The office has not stated that Kyriazis is equivalent to applicant’s claimed invention or that the mice taught by Kyriazis et al. have the exact same properties as the mice or rodents claimed by applicants. As stated in the previous office action, Kyriazis et al. differs from the instant invention as claimed by failing to teach orthotopic transplantation of the human tumor pieces. Wang et al. and McLemore

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et al. were cited to provide teachings and motivation for substituting orthotopic transplantation of the tumor pieces for subcutaneous transplantation.

Regarding Otto et al., the previous office action only cited Otto et al. for teaching that the growth of human renal cell carcinoma embedded in renal tissue from nephrectomized patients that had been transplanted into nude mice correlated well with the clinical course of the patients. Since Kyriazis et al. did not specifically test a human renal tumor, Otto et al. was simply cited to demonstrate that human renal tumors grown in nude mice also recapitulate the growth characteristics observed in human patients. Contrary to applicant's assertion that Otto et al. does not make the statement that tumor pieces transplanted into nude mice "correlate well with the clinical course of the patients", Otto et al. does indeed make this statement. The applicant is directed to page 173 of Otto et al., column 2, lines 8-10, which states that, "Our previous data show that tumor growth in this model correlates well with the clinical course of the patients-an indication that this is a reliable experimental model". The fact that Otto et al. does not teach or suggest specifically looking for and following the progression of metastasis in this paper is irrelevant, since Kyriazis et al., the primary reference, already provides this teaching, and Otto et al. has only been cited to demonstrate that human renal tumors, like all the other tumors taught by Kyriazis et al., grow well in nude mice and in a fashion which mimics the growth of these tumors in humans. As noted above, the claims as written simply recite that the mouse or rodent, "has sufficient immunodeficiency to allow said transplanted neoplastic tissue to grow and metastasize, so as to mimic the progression of the neoplastic disease in the human donor".

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The previous office action stated that neither Kyriazis et al. nor Otto et al. specifically teach the orthotopic transplantation of human tissue to nude mice. Wang et al. has been cited to supplement Kyriazis and Otto by teaching that the orthotopic transplantation of colonic tumors, maintained in nude mice, into the colonic wall of naive nude mice results in growth and metastasis of the colonic tumors which mimics the pattern of metastasis observed in the original human patients (Wang et al., page 331, abstract). McLemore et al. has also been cited for teaching an athymic nude mouse model for human lung cancer, wherein nude mice receive orthotopic transplantation of several different human lung carcinoma cells lines intrabronchially (McLemore et al., page 5133, column 2 paragraphs 2-4). McLemore et al. has further been cited as providing motivation for using orthotopic transplantation versus subcutaneous transplantation of human tumors in nude mice by demonstrating that mice transplanted intrabronchially with lung tumor cells demonstrated increased rates of growth and metastases than those transplanted subcutaneously (McLemore et al., page 5132, abstract, and 5133, Table 1).

The applicant argues that Wang does not in fact say anything about the progress of the disease or metastasis following orthotopic injection of colonic tumors. The office disagrees with this assessment of the teachings of Wang et al. Wang et al. first states that subcutaneous implantation of human colorectal tumors results in minimal or absent locoregional tumor invasion and infiltration, see the first sentence of Wang et al. abstract. Wang et al. then teaches that in contrast to subcutaneous implantation, orthotopic implantation of the colonic tumors into the colonic wall resulted in tumor invasion of “ various subregions of the colonic wall and mimicked

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the original pattern characteristic for patient tumors” (Wang et al., page 331, lines 11-14). The very next line goes on to say that, “A propensity for tumor cells to grow within lymphatics and to a lesser degree within veins was observed” (Wang et al., page 331, lines 15-17). Applicant’s confusion over the “reference point” of this sentence seems misplaced since the sentence clearly follows the description of what happens in the nude mouse following orthotopic implantation of the colonic tumor. There is no confusion over which tumor cells they are referring to. Further, the ordinary artisan at the time of filing would have had no trouble understanding that growth of tumor cells in lymphatics following colonic implantation is an example of tumor metastasis. Finally, the fact that the **primary** tumors established following subcutaneous versus colonic implantation did not apparently have different rates of growth does not affect the central teachings of Wang et al. that orthotopic implantation of colonic tumors provides tumor growth patterns which more closely mimic that of human patients.

Furthermore, the office did not simply rely on the teachings of Wang et al. for motivation to implant human tumors orthotopically rather than subcutaneously in nude mice. McLemore et al. was further cited. Regarding McLemore et al., the applicant argues that most of the examples in McLemore do not represent orthotopic transplantation and that the results obtained by McLemore following orthotopic implantation of lung tumor cells to the lung show only 3% metastasis. The applicant therefore concludes that McLemore does not demonstrate that an accurate model of human disease would be obtained using the McLemore methodology. In response, the applicant is reminded that the rejection of record is not based on solely on the

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teachings of McLemore. The office has not and does not suggest that McLemore alone teaches the applicant's claimed invention. Instead, the office has cited McLemore for teaching the advantages of orthotopic implantation of human tumors in athymic mice over subcutaneous injection of tumors. Table 1 on page 5133 of McLemore et al. clearly demonstrates that orthotopic implantation of human lung tumor cells vastly improves the propagation of the human tumors in nude mice over subcutaneous implantation. McLemore reports that human lung tumors implanted into the lung show micro and macro invasion of the lung and further are capable of metastasis. Furthermore, the rate of metastasis is not relevant to applicant's invention as claimed. The claims as written recite an immunodeficient rodent model for human neoplastic disease. The only reference to metastasis in these claims read as follows, "allowing said transplanted tissue to grow and metastasize". There are no limitations in the claims regarding rates of metastasis. In fact, the claims as written are not even specifically directed to following the progression of metastasis. Instead, the claims as written are directed to rodent models of human neoplastic disease. Neoplastic disease encompasses metastatic cancer, but is not so limited. Neoplastic disease refers to cells which evolve to exhibit inappropriate growth characteristics.

Furthermore, contrary to applicant's argument that there is no motivation to combine the teachings of Kyriazis and Otto with Wang and McLemore, both Wang et al. and McLemore et al., as discussed in detail above, provide substantial motivation to substitute orthotopic implantation of human tumors for the subcutaneous implantation method used by Kyriazis et al. Both Wang et al. and McLemore et al. clearly teach that orthotopic implantation increases human tumor

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propagation frequency and growth in nude mice and further more closely mimics the growth pattern of the tumors in humans. The applicant also errs by stating that none of the documents recognizes that there is any inadequacy in the tumor models at the time of filing. On the contrary, McLemore et al. provides a detailed discussion of problems associated with using human xenograft tumors in nude mice as a model for human disease and specifically suggests that orthotopic implantation of the human tumors is one method of improving the utility of nude mouse models as models for the study of human disease (McLemore et al., page 5132, column 2, paragraphs 2-3). Thus, in view of the motivation provided by McLemore et al. and Wang et al. that orthotopic implantation of tumor cells results in the growth of human tumors in mice that mimics the growth patterns of the human tumors in human patients and that human tumors implanted orthotopically demonstrate increased rates of growth compared to tumors transplanted subcutaneously, it would have been *prima facie* obvious to the skilled artisan to substitute orthotopic implantation for subcutaneous implantation in the method of generating a nude mouse model of human cancer taught by Kyriazis et al. and Otto et al. Furthermore, based on the teachings of Otto et al. and Kyriazis et al. that intact tumor tissue maintains growth and morphological characteristics in the nude mouse, and the teachings of Wang et al. and McLemore et al. that orthotopic transplantation in nude mice versus subcutaneous transplantation more closely mimics the growth and metastases of human tumors in patients, the skilled artisan would have had a reasonable expectation of success in generating and using a nude mouse model for

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human neoplastic disease which mimics the growth and metastasis of the human tumors in patients characterized by orthotopically transplanted intact human colon, lung, or breast tissue.

In addition, as the art of record teaches that many different types of tumor tissue, including colonic, lung, renal, pancreatic, laryngeal, and bladder tissue, can be transplanted orthotopically into mice to generate a mouse model for human neoplastic disease, it would have been *prima facie* obvious to the skilled artisan to generate a nude mouse model for any type of human cancer, including ovarian cancer, by implanting the human neoplastic tissue into the analogous murine tissue. Therefore, in view of the high level of surgical skill in transplanting tissue into mice at the time of filing, the motivation to generate mouse models for many different kinds of human tumors by orthotopically transplanting human tumor tissue to nude or immunodeficient mice as provided by Wang et al., McLemore et al., and Otto et al., the skilled artisan would have had a reasonable expectation of success in implanting neoplastic human ovarian tissue into murine ovarian tissue in order to produce a murine model for human ovarian neoplastic disease.

Finally, the applicant argues that the reliability of the instant methods to produce metastases of human tumors in nude mice and the pattern of metastasis observed by applicants represent an unexpected result over the teachings of the prior art. However, the claims do not recite any particular limitation regarding the frequency with which mice produced using the instant methodology generate metastases. The claims do not recite that the methods have to be 100% effect, or recite any specific limitation regarding the metastatic growth patterns of the

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implanted tumors or the time course over which the disease course is to be followed. The claims simply recite that the implanted tumor “mimics the progression of the neoplastic disease in the rodent”. Wang explicitly teaches that the disclosed nude mouse model does just that. Further, Kyriazis et al. clearly demonstrates that the implantation of intact pieces of human tumors into nude mice consistently generates metastases in the same organs that show metastasis in humans. In addition, in regards to claims directed to the nude mouse model itself, the efficiency of the method of making the mouse are not relevant to the patentability of the claims as long as the mouse itself is taught or suggested by the prior art. See *In re Thorpe*, cited in the previous office action. Therefore, for reasons of record as discussed in detail above, the rejection of record is maintained.

The rejection of claims 14, 16, 21, and 23 under 35 U.S.C. 103(a) as being unpatentable over Kyriazis et al. (1981) Canc. Res., Vol. 41, 3995-4000 in view of Otto et al. (1985) J. Urol., Vol. 134, 170-174, Wang et al. (1982) Exp. Cell. Biol., Vol. 50, 330-331, and McLemore et al. (1987) Cancer Research, Vol. 47(19), 5132-5140 as applied to claims 1-13, 15, 17-18, 20, 22, 24, 27-28, 30-37, 42-49, and 54-61 above, and further in view of Giovanella et al. (1984) Exp. Cell. Biol., Vol. 52, 76-79, is maintained. The applicant has not presented any arguments in regards to this rejection. Arguments regarding the teachings of Kyriazis et al., Otto et al., Wang et al., and McLemore et al. have been addressed in detail above and have not been found persuasive. No

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arguments regarding the teachings of Giovanella et al. have been provided. Therefore, the rejection of record stands.

The rejection of claims 18 and 25 under 35 U.S.C. 103(a) as being unpatentable over Kyriazis et al. (1981) Canc. Res., Vol. 41, 3995-4000 in view of Otto et al. (1985) J. Urol., Vol. 134, 170-174, Wang et al. (1982) Exp. Cell. Biol., Vol. 50, 330-331, and McLemore et al. (1987) Cancer Research, Vol. 47(19), 5132-5140 as applied to claims 1-13, 15, 17-18, 20, 22, 24, 27-28, 30-37, 42-49, and 54-61 above, and further in view of Reddy et al. (1987) Cancer Res., Vol. 47 (9), 2456-2460, is maintained. The applicant has not presented any arguments in regards to this rejection. Arguments regarding the teachings of Kyriazis et al., Otto et al., Wang et al., and McLemore et al. have been addressed in detail above and have not been found persuasive. No arguments regarding the teachings of Giovanella et al. have been provided. Therefore, the rejection of record stands.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to be 'Anne M. Wehbé', with a long horizontal stroke extending to the right.